Official Title: Duration of Brace Wear in Clubfoot Treatment – A Prospective Randomized Trial

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Duration of Brace Wear in Clubfoot Treatment – A Prospective Randomized Trial

RESEARCH DESIGN AND METHODS

Aim 1

a. Establish the time dependent risk for relapse with need for further therapy in isolated clubfoot for 2 year versus 4 year bracing.
b. Determine whether covariates that include compliance with bracing, gender, age, severity, and family history are associated with relapse.

Rationale

Based on the hypothesis that prolonged bracing will reduce clubfoot recurrence, we propose a multi-center, randomized, controlled trial evaluating the effectiveness of a 2 year versus 4 year bracing protocol in preventing clubfoot recurrence. No studies have previously assessed the length of bracing necessary to prevent clubfoot recurrence; therefore, the results of this study will have great clinical utility. When designing this trial, we sought to balance rigor with feasibility, and to maximize internal validity without sacrificing external validity.

Sample Size Justification and Statistical Power

The primary goal of this project is to determine the rate at which clubfoot recurs during the first year post-treatment. Because this primary goal involves estimation, we discuss sample size issues from the perspective of confidence bounds. ***Table 1 presents the statistical power to detect between-group differences for various recurrence rates with the target enrollment sample size of 62 patients per group. Assuming a 10% dropout rate, with a total enrollment of 124 patients (55/group completing the entire trial) and observed recurrence rates of 10% versus 45%, statistical power will be excellent (0.99) to detect this between-group difference in recurrence rate of at least 35%.*** That is, with 95% certainty, our estimate of the between-group difference in recurrence rate will be within 15% (50%-20%/2) of the true rate difference. Even with a more conservative estimate of the between-group difference, the study will have adequate power (0.80) to detect a between-group difference as small as 21%; where the recurrence rate in one group is 10% and the recurrence rate in the other group is as small as 31%.

Two comments about the above computations are in order. First, we have estimated confidence bound widths using proportions instead of the Kaplan-Meier survival curves we will use in practice when we analyze the data. The reason is that we have no way at this time to estimate the standard errors that will result from the survival curves. During the early portions of the curve when we have complete data, we anticipate that the confidence bounds generated by the survival curves will be narrower than those presented above. By contrast, it is possible that the confidence bounds we generate for later portions of the curve may be wider than those presented above given the presumed number of dropouts. Second, we believe that independent of the standard errors resulting from the survival curves, our computed confidence bound widths are inherently conservative (i.e. we may get

narrower bounds in practice). The reason is that we anticipate in practice that the true dropout rate, particularly at earlier time points, will be less than the 10% that has been used in computing the number of subjects who provide data. Study dropouts will increase the study power because they will provide useful data up to the point of dropout. Thus, we believe that the presented power computations based on the sample of patients that complete the trial are conservative.

In addition to the reasons already presented, the provided power computations ensure a conservative estimate of sample size because they (1) utilize reoccurrence rates through 12 months of follow-up data only, and more patients will reoccur over time, and (2) have been performed using a dichotomous outcome measure whereas the data will be analyzed using survival analysis where follow-up on many patients will exceed 12 months. The primary analysis will enhance power by applying survival models and using a log rank test to compare time to reoccurrence between treatment groups.

Table 1. Recurrence rate between-group differences detectable with alternative incidences and a target enrollment of 124 patients (62 per group). Estimates based on two-tailed tests at alpha=0.05 comparing the rate of the event in two groups.

# of Patients in each Group		Detectable Relapse Rate at Specified Sample Size and Power			Power
Enrolled	With Complete Data*	Group 1	Group 2	Between-Group Difference (95% CI)	
62	55	10%	45%	35% (20%, 50%)	0.99
			40%	30% (15%, 45%)	0.96
			31%	21% (6%, 36%)	0.80

CI = confidence interval. *After adjusting for a 10% loss to follow-up.

Sufficient patient recruitment is essential to the feasibility of a clinical trial. To determine whether we could achieve a target enrollment of 124 patients based on power analysis described above, we asked potential centers to perform a chart review of all clubfoot patients seen in a recent and representative 3-month period of time. Investigators determined those patients who met eligibility requirements, and recorded the following information on a standard datasheet: gender, age, Pirani score, and language spoken. Ten centers sent us estimates ranging from 10 to 30 patients per 3-month period.

In addition to the PI's St Louis Shriners Hospital, six centers were selected based on a high recruitment potential and our previous experience with these centers in other ongoing research studies. **Assuming a 25 percent randomization rate, these data indicate that the seven participating centers could effectively recruit 124 subjects in a 12-month period.**

Experimental Design

A day-long training session will be used to instruct the investigators, coordinators, and orthotists on all aspects of the trial that are outlined below.

1. Inclusion and Exclusion Criteria

Patients must be less than one year of age and diagnosed with isolated clubfoot in order to be included in the study. Strict criteria will be used to establish the diagnosis of clubfoot. Specifically, at least one foot must demonstrate fixation of the foot in equinus, forefoot adduction, cavus, and hindfoot varus and the abnormality must be present at birth (i.e. congenital). Patients with metatarsus adductus or positional talipes are not considered to have clubfoot and are excluded from the study. Patients may have begun casting at the time of enrollment, but foot abduction bracing may not have already been started.

Only patients with isolated clubfoot are included in this study. Patients with dysmorphic features, additional anomalies (i.e. congenital heart disease, hypospadias), or developmental delay are excluded from the study. Neurologic causes for clubfoot will be ruled out in all patients through careful examinations. Based on our prior use of these criteria, 76% of our patient population will be considered to have isolated clubfoot (Gurnett et al. 2008b).

2. Randomization and Data Collection

Randomization will be stratified by sex (male/female) and laterality (unilateral/bilateral) within each clinical site. Within each stratum, patients will be allocated in a 1:1 ratio to either 2-year or 4-year bracing using a variable block size to ensure that there is no temporal bias and that the two study arms will be balanced by gender and laterality within each site. Randomization sequences will be generated with SAS software (SAS Institute Inc., Cary, NC, USA) by the study statistician *a priori.* When a participant is ready to be randomized, the site coordinator will access a secure and password-protected website, provide the participant's study ID number, identify the appropriate stratum, and verify that the participant fulfills the eligibility requirements. The website will then access the randomization sequence for that stratum, determine the next treatment assignment, and elicit the treatment assignment. A study subject will be randomized and assigned to treatment only when it has been determined that he/she has satisfied all the eligibility requirements for the study and informed consent for the intervention phase has been obtained.

To ensure that we are collecting quality data, we developed valid and logically consistent case report forms that will be used in these studies. Clinical information includes severity (Pirani score), age at treatment initiation, sex, laterality, family history of clubfoot in first degree relative, number of casts required to treat, use of tenotomy, and the presence of the drop toe sign (Edmonds and Frick 2009). Individuals collecting and entering data will be adequately trained, and data will be monitored to ensure that the database is accurate. The coordinator will download the data from the dose monitor at each 3-month visit, and re-launch it so it can be remounted by the orthotist. The data will be saved as a comma delimited file and the file will be uploaded into the data entry system by the site coordinator..

3. Casting and Bracing Protocol

The Ponseti method of casting will be followed and all PI's are Ponseti certified physicians. Tenotomy will be performed before last cast application for any foot that cannot achieve at least 10° of ankle dorsiflexion as measured with a hand-held goniometer. The foot will be considered corrected if greater than 50° of foot abduction and greater than 10° of ankle dorsiflexion can be achieved, both measured with hand-held goniometer. Those feet that

are not fully corrected will undergo further casting until correction is achieved before starting the bracing protocol. The number of casts required to achieve correction will be recorded as well as any casting complications. After achieving correction all patients are fitted **with a foot abduction brace (FAB) consisting of shoes attached to a bar**. The type of FAB used will be based on physician and family preference but the common factor between all braces will be the presence of a bar connecting the shoes. The presence of a bar has been shown to be the crucial feature of clubfoot bracing (Janicki 2011). All caregivers will be instructed to place child in the FAB 23 hours a day for three months and then night time use (eight to twelve hours) hours a day for 2 versus 4 years based on treatment arm. All braces will include an implanted temperature logger that will be launched by the research coordinator prior to mounting.

All centers will provide the names and credentials of the orthotists they plan to work with for the study. The orthotist will adjust pads, areas of relief, and straps as needed to optimize fit. Clubfoot recurrence will be determined by the treating physician and treated with repeat casting followed by FAB use. Recurrence is defined as the development of any of the following deformities in isolation or in combination that require repeat cast application or surgical intervention: hindfoot varus, hindfoot equinus, forefoot adduction, forefoot cavus, or forefoot.

The Coordinating Center will develop manuals of operations to standardize patient management. However, variability in practices is allowed and will be at the discretion of the physician and orthotist at each clinical site. This may impart some variation in care across the centers, but will realistically mimic the current state of the art for the best care possible. Randomization within sites will minimize the potential bias introduced by differences in patient populations and management across sites and orthotists

4. Follow-Up Schedule

Study subjects will be seen every 3 months. Interim visits for brace fitting and consultation or family discussions with the physician/coordinator/orthotist will be allowed and encouraged. Local coordinators will contact the patient and family via phone at least monthly to provide the opportunity for questions, discussion, and feedback as needed. Subjects will be evaluated at each visit of the current state of their clubfoot and will be told if there are any signs of recurrence. Parents have the right to withdraw from the study at anytime.

5. Study Endpoint

Although follow-up data will be collected for the duration of the trial, the data collected at 1-year follow-up post completion of treatment arms will be used for the primary analysis to address the question asked in specific aim 1a. This ensures that patients in both treatment arms are followed for the same amount of time after they finish bracing.

6. Statistical Analysis

General

The goal of this study is to establish the time-dependent risk for recurrence within the first year post-treatment and evaluate factors associated with recurrence in isolated clubfoot. Kaplan-Meier survival curves that describe the time to recurrence will be generated, with

95% confidence bounds placed around the probabilities that this event will occur at pre-defined intervals. Of particular interest will be an assessment of the hazard ratio, with 95% confidence bounds, that compares recurrence in patients receiving 2-year versus 4-year bracing. While the goal of this study is to detect an overall treatment difference, Cox regression analysis will determine whether covariates that include compliance with bracing, gender, laterality, age, Pirani score, and family history are associated with the probability that relapse will occur. A separate Cox model will be used for each covariate.

Additional analyses include mixed model repeated measures analysis of variance to determine if the magnitude of changes in exam findings differs according to whether a recurrence ultimately occurs. Unlike traditional repeated measures analyses, the mixed model method allows for the inclusion of patients with incomplete data. The focus of these analyses will be the interaction between recurrence group and time point; interactions that test hypotheses regarding the equality of changes over time in the two groups. Within the mixed model, appropriate statistical contrasts will be used to test the null hypothesis that changes between two specific time points in one group are equal to corresponding changes in another group.

Simple t-tests and chi-square tests will be used to determine if characteristics at study enrollment differ according to whether there is recurrence. Receiver operating characteristic (ROC) curve analysis will be performed to determine if measures of compliance discriminate patients that recurrence from patients that do not recurrence.

These data will be analyzed with an “intention to treat” principle; wherein patients will be included in the intervention group as determined by the randomization, independent of compliance. Secondary analyses will be performed to evaluate the effects of treatment independent of crossover by examining outcomes relative to actual treatment status.

For all analyses, careful attention will be given to whether the data satisfy the distributional and model-specific assumptions of the procedures used. Appropriate data transformations or non-parametric methods will be used as appropriate.

It is important to point out that this study is not designed to (1) assess the safety or efficacy of a particular brace; (2) compare outcomes across clinical sites. All sites will use foot abduction braces. To avoid any perception of conflict of interest and to follow recommendations from the Disclosure Review Committee, the type of particular brace used will not be recorded in the study data. Brace type is inherently associated with clinical site and site physician. As such, the following variables will not be included as effects of interest in the analytic models: brace type, clinical site, physician, and orthotist.

Heat sensor data (analysis)

While previous studies by our group and others have demonstrated that brace noncompliance is the number one risk factor for recurrence (Dobbs et al. 2004), these conclusions were made without objective measures of brace compliance. In prior studies, brace dose has been addressed simply as "compliance" or as an average number of hours worn.

Because we will use a heat sensor to objectively and accurately monitor compliance, compliance may be evaluated as both a continuous and a dichotomized measure. First, we will calculate the area under the curve to create one summary measure per patient per study period (or across the entire intervention period) as a continuous variable (i.e. average hours worn). For each individual, an area under the hours worn curve will be computed and the areas compared across between groups of patients who recurrence and those who do not. Second, we will analyze compliance as a dichotomized variable. For example, an adherer is someone who wears the brace for at least 80% of the prescribed time. The percentage of each group (recurrent patients versus non-recurrent group) who adhere to bracing regimen during each study time period (or across the entire intervention period) will be compared. Simple t-tests will be used to compare each group.

7. Data Management and Quality Control Activities

The first three months of this study will be spent establishing the infrastructure necessary to assemble data. ***[The coordinator will need time to train personnel at participating site]***. Prior to study start, the Coordinating Center (CC) will develop a data quality assurance plan and develop quality control procedures (QC) in accordance with the plan. The CC Research Coordinator will develop a Manual of Procedures (MOP) to address enrollment, patient safety monitoring, adherence to study procedures and timelines, and to facilitate consistency in protocol implementation and data collection across clinical sites. The MOP will specify the methods by which data is to be collected and related quality assurance procedures. The CC Coordinator will also provide dynamic training and certification of personnel across sites to ensure standardization of procedures.

All study measurements will be performed by the clinical sites on paper case report forms (CRFs) developed and maintained by the CC. Paper CRFs provide the vehicle for standardized and consistent collection of data prior to online data entry, and are converted to electronic data using the REDCap Web Based Data Capture System for data entry. Each site will be responsible for reviewing completed CRFs for accuracy and completeness, and entering their data into the REDCap system. REDCap provides secure, web-based applications with an intuitive interface for users to enter data and have real time validation rules such as range checks for categorical and continuous variables, automatic branching logic, checks for internal consistency within a form, and calculation of derived variables. REDCap servers are securely housed in an on-site limited access data center managed by the Division of Biostatistics at Washington University. All web-based information transmission is encrypted. Separate QC programs will be written to verify that study identification numbers are accurately labeled throughout the various forms, longitudinal checks to evaluate consistency over time, and checks for incomplete data. These checks will be performed routinely by the Study Statistician. Problem data will be reported to the Coordinator for investigation and resolution. Data sets that contain personal identifiers will be encrypted and password protected.

The Study Statistician will perform routine reporting duties to monitor recruitment and retention, overall data quality and status, and protocol deviations; as well as perform formal statistical analyses.

The CC Coordinator will perform all organizational and recording tasks that surround study meetings, conference calls, and site visits. In addition, at periodic intervals during the study,

the CC Coordinator will conduct on-site monitoring visits and perform source document verification.

Possible outcomes, interpretations, and contingency plans

1. Patient Enrollment
Each site is expected to enroll the number of subjects that have been outlined above to retain project funding. Recruitment reports will be generated by the lead site on a monthly basis, and formal reviews will be conducted at the end of Year 1, and then monthly after that until all subjects are enrolled. In the case of low enrollment (less than 1 subject per month), the PI will personally visit the center to determine if procedures are in place to maximize recruitment and will determine whether the situation is reparable. The sites not chosen initially will serve as alternative sites to participate if necessary. Four additional centers have expressed desire to participate and are therefore available for participation if recruitment goals are not met in a timely fashion.

Low participation rates and other threats to external validity are also problems common to every randomized controlled trial. The randomization simulation indicates the most prevalent reason for non-participation was the wish to make a shared decision concerning treatment and participation. Based on these results, we will encourage discussion between the parent and physician. Additionally, we will emphasize in all stages of recruitment that the physician is participating in this study because she/he cannot recommend one treatment arm over the other based on the current state of the science regarding bracing.

If, after the first review, it is determined the power of the study will be compromised due to low enrollment, and if low enrollment is due to patients' desire NOT to randomize, we will consider adding a restricted cohort parallel trial in which eligible patients who decline randomization will be asked to enroll in an observational arm where they are free to choose between the two treatment arms. All facets of the protocol will be implemented except randomization. This restricted cohort design has been recommended by several authors, and a variation of it is being used in the SPORT study headed by James Weinstein. A separate set of analyses would be conducted for the observational cohort, again using intention-to-treat, and as-treated analyses. Because the treatment groups will not be balanced by randomization, we would use propensity score analysis to control for the propensity to choose one treatment over another. The propensity score enters the regression equation, allowing for a straightforward evaluation of the estimated treatment versus control effects that reflect adjustment of differences in observed background characteristics. This method has been widely used in health services and clinical research as an alternative to randomized designs (Brener et al. 2004).

2. Crossovers, Dropouts, and Subjects Lost to Follow-Up
Subjects/parents requesting crossover or to exit the study will have their questions and concerns addressed. Both options will be allowed in deference to the subject's right to self-determination. However, neither option will be suggested or encouraged by any member of the team. All participants, regardless of crossover to an alternate treatment or study dropout will follow all other study procedures to the study end, unless a participant refuses to continue in the study by withdrawing his/her consent. In the intention-to-treat analysis, subjects will be analyzed in the treatment to which they were randomized.

An "as-treated" analysis will be performed in addition to the primary intention-to-treat analysis to take into account the effect of crossover and dropout. It should be remembered that crossover occurs in the typical clinical setting whenever the patient either doesn't wear the brace at all, wears the brace at a less-than-effective dose, or when the patient or physician requests a brace after a period of observation. If a subject crosses over from observation to bracing treatment, we will be able to account for the patient's characteristics at the time of cross-over, and the dose monitor will allow measurement of subsequent time in brace. A 10 percent lost-to-follow-up rate has been taken into account in the sample size/power calculations. Although unrealistic, only a 0% rate of loss to follow-up guarantees the benefits of randomization. We will employ several proven strategies to minimize loss to follow-up, including education concerning the full burden of trial participation, minimization of respondent burden in terms of visits and questionnaires, obtaining at least one alternative contact for each subject, as well as phone calls and other reminders of upcoming visits. The seven centers have a documented ability to cover a 15% rate of dropout that is 5% greater than the estimate used for planning purposes. If dropouts exceed this during the recruitment phase, then centers from the alternate list will be brought into the study. If excessive dropouts occur during the follow-up phase of the study, no additional centers will be recruited and instead, attempts to locate the patient and determine final outcome will be made, and if needed, statistical methods will be employed to compensate for missing data.

Summary of Research Proposal

Clubfoot is a common and severe musculoskeletal birth defect. Although clubfoot is often successfully treated with the Ponseti method, some clubfeet relapse in the following years. One goal of this study is to provide clinically useful information regarding the optimal length of abduction bracing that is necessary to prevent clubfoot recurrence. A second goal of this study is to investigate the other variables (clinical, bracing compliance) that influence clubfoot recurrences. These studies have great potential to impact the care and treatment of patients with clubfoot.